

**REMARKS**

Claims 1, 5, 8, 21, and 23-67 are pending and under consideration, prior to Amendment.

Claim 60 has been amended to point out that the method includes ascertaining whether colon cancer tissue expresses a *gli-1* gene. Claim 63 has been amended to point out that the method includes ascertaining whether colon cancer tissue expresses a *Sonic hedgehog* gene. Claim 64 has been amended to point out that the method includes ascertaining whether the tumor expresses a *Sonic hedgehog* gene. Additionally, claims 60, 61, 63, and 64 have been amended to clarify that the colon cancer tissue expresses a *gli-1* or *Sonic hedgehog* gene. Support for Applicants' amendments can be found, for example, in Examples 5 and 8. No new matter has been entered.

Applicants note with appreciation that claims 1, 5, 21 and 23-60 are allowable with respect to the elected species of "colon cancer."

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the Office Action.

**Continued Examination Under 37 CFR 1.114**

Applicants note that the finality of the previous Office Action has been withdrawn in view of Applicants' Request for Continued Examination. Applicants note that the submission filed June 11, 2008 has been entered in full.

**Information Disclosure Statement**

Applicants note that the Information Disclosure Statement filed June 11, 2008 has been considered.

**Withdrawn Rejections**

Applicants note that the provisional rejection of claims 1, 5, 21, and 23-60 under the judicially created doctrine of obviousness-type double patenting (with respect to the elected species of colon cancer) has been withdrawn.

Applicants note that the Examiner has indicated that claims 1, 5, 21, and 23-60 are allowable with respect to the elected species of "colon cancer", and that examination will now be extended. Extension of examination to include, for example, "bladder" and "prostate" necessitated a provisional obviousness-type double patenting rejection, which is detailed below.

**35 U.S.C. § 112, 1st paragraph, enablement**

Claims 60 and 63-67 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

Applicants point out that the specification discloses methods that do not involve a first step of determining whether the cells overexpress gli-1 or Sonic hedgehog, but nonetheless demonstrate that the hedgehog antibody effectively treats unwanted cell proliferation and growth in tumors that express Sonic hedgehog. In example 5, bladder cancer cells were injected into nude mice to induce tumor formation. Subsequently, the mice were treated with either the hedgehog antibody 5E1, or a control IgG antibody. This method did not include any step of determining gli-1 or Sonic hedgehog gene expression, but treatment with 5E1 still proved effective at reducing the size of the tumor. Notably, these particular tumors likely express Sonic hedgehog, because the tumors were generated from the RT-4 cell line, which expresses Sonic hedgehog (Fig. 19).

Example 8 discloses another experiment in which a tumor was successfully treated with 5E1 without requiring a first step of determining gli-1 or Sonic hedgehog gene expression. Here, hedgehog-expressing colon cancer cells were used to generate the animal model of colon cancer, but neither gli-1 nor Sonic hedgehog gene expression was determined at any point before, during, or after treatment with 5E1. Nonetheless, the method of treatment with 5E1 proved to be effective at decreasing the size and rate of growth of the tumors.

In both examples, cancer tissues expressed Sonic hedgehog, but a step for determining Sonic hedgehog levels was not part of the treatment method. Thus, Applicants maintain that the specification clearly teaches that the determination step is not needed for successful treatment of a cancer that expresses Sonic hedgehog. One of skill in the art would readily recognize that information about gli-1 or Sonic hedgehog expression levels could be obtained from a wide variety

of sources, and thus a step of determining expression would not be necessary to enable the claimed invention.

Nevertheless, to expedite prosecution, Applicants have amended claims 60, 63, and 64 (and claims depending therefrom) to more particularly point out certain embodiments of the claimed invention. Specifically, claim 60 has been amended to point out that the method includes ascertaining whether colon cancer tissue expresses a *gli-1* gene. Claim 63 has been amended to point out that the method includes ascertaining whether the colon cancer tissue expresses a *Sonic hedgehog* gene. Claim 64 has been amended to point out that the method includes ascertaining whether the tumor expresses a *Sonic hedgehog* gene. Applicants additionally note that claims 60, 63, and 64 have been amended to clarify that the colon cancer tissue expresses (rather than overexpresses – which implies a comparison to some other current or stock sample tissue) a *gli-1* or *Sonic hedgehog* gene. Support for Applicants' amendments can be found, for example, in Examples 5 and 8, in which expression of *gli-1* or *Sonic hedgehog* in the tumors was not actively determined as part of the method of treatment, but rather, had been established (e.g., ascertained) by other means.

Applicants' amendments are not in acquiescence to the rejection, but are believed to obviate the rejection. Applicants expressly reserve the right to prosecute claims of similar or differing scope in this or future application. Reconsideration and withdrawal of this rejection are requested.

### **35 U.S.C § 112, 2nd paragraph**

Claims 60, 63-67 are rejected under 35 U.S.C § 112, second paragraph, as allegedly omitting essential steps that would particularly point out and distinctly claim the claimed invention. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

Applicants contend that the claims, prior to amendment, were clear. Nevertheless, to expedite prosecution, and as detailed above in response to the enablement rejection, Applicants have amended claims 60, 63, and 64 to include ascertaining whether colon cancer tissue expresses ... a *gli-1* gene (in the case of claim 60) or a *Sonic hedgehog* gene (in the case of claims 63 and 64). Applicants' amendments are not in acquiescence to the rejection, but are believed to obviate the

rejection. Applicants expressly reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are requested.

**35 U.S.C. § 112, 1st paragraph, new matter**

Claims 61-67 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. According to the Examiner, the specification allegedly lacks support for independent claim 61 and its dependent claim 62, because the specification teaches methods related to determining overexpression of gli-1 but not Sonic hedgehog. The Examiner further asserts that the specification lacks written description for independent claims 63 and 64, and all claims depending therefrom, because the specification is allegedly missing the teaching of a method of administering an antibody to a patient having colon cancer that overexpresses a Sonic hedgehog gene. Applicants respectfully traverse the rejection.

Claim 61 satisfies the written description requirement, as detailed in MPEP 2163 (I): "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Sufficient details of the invention abound. Paragraph [0023] establishes that there are methods and reagents for reducing undesirable cell growth in cells with an active hedgehog signaling pathway. Paragraphs [0055], [0061] and [0062] refer to figures showing overexpression of shh and gli-1 in two examples of undesirable cell growth: prostate cancer cell lines and benign prostatic hyperplasia. Paragraph [0066] provides an overview of the present invention, and states that hedgehog antagonists can, at least in part, inhibit the signal transduction pathways regulated by hedgehog and other proteins. Paragraphs [0715]-[0717] describe how shh and gli-1 levels were measured in samples of human bladder cancer, and were found to be overexpressed, relative to control bladder tissue. Examples 5, 6, and 8 disclose the administration of 5E1 to cancer cell lines and animal models of cancer, and a consequent decrease in the growth and proliferation of cancer cell lines and tumors. Finally, paragraph [0685] discloses some of the types of cancer in which hedgehog signaling plays a causative role, including prostate and breast cancer, as well as benign prostatic hyperplasia. Taken together, these paragraphs would lead one of skill in the art to conclude that Applicants (1) had methods for determining whether tumors express

a Sonic hedgehog gene, (2) knew that hedgehog antagonists could be used to inhibit the effects of hedgehog signaling, (3) could administer hedgehog antibodies to subjects and (4) could expect tumors that express Sonic hedgehog to show decreased cell growth or proliferation after treatment with hedgehog antibodies. All of these elements are recited together in claim 61. Applicants point out that the adequate description requirement for a claim is met when "a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claim is not explicitly described in the specification." See e.g. *Vas-Cath*, 935 F.2d at 1563, 19USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

Claims 63 and 64, and claims depending therefrom, are also supported by the specification. Examples 5 and 8 detail how cancer cells that express Sonic hedgehog are used to create an animal model of cancer, after which administration of 5E1 leads to a decrease in tumor size and rate of growth. In both examples, tumors in the animal models were derived from cell lines that express Sonic hedgehog, and thus the specification teaches a method of treatment that includes administering an antibody to a subject having colon cancer that expresses a Sonic hedgehog gene.

Applicants contend that claims 61-67 are amply support by the specification and that no new matter has been added by presentation of these claims. Reconsideration and withdrawal of this rejection are requested.

### **Double Patenting**

Claims 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38, 40-43, 50-53, 56, 57, and 64-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claim 68 of co-pending Application No. 10/652,298. Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Applicants note that, in accordance with MPEP 804.I.B, the Examiner will maintain the provisional double patenting rejection until there are either no longer any conflicting claims or the double patenting rejection is the only remaining rejection in at least one of the applications.

**Co-Pending Applications**

The Examiner is obviously aware of co-pending Application No. 10/652,298 (currently applied in the above noted double patenting rejection). Applicants invite the Examiner to consider all prior, ongoing, and future prosecution of co-pending Application 10/652,298 (the most recent action is a non-final Office Action, mailed on August 29, 2008).

Additionally, Applicants take this opportunity to update the Examiner on the status of various co-pending applications – the existence of which has already been brought to the Examiner's attention and made of record in this case. Applicants invite the Examiner to consider all prior, ongoing, and future prosecution in these co-pending applications. Application serial number 09/804,490 issued November 4, 2008 as US Patent No. 7445778. The most recent action in application serial number 10/652,686 is a Notice of Allowance mailed October 7, 2008. The most recent action in application serial number 09/883,848 is a Final Office Action mailed March 3, 2008. The most recent action in application serial number 10/772,090 is a Non-final Office Action mailed October 9, 2008. The most recent action in application serial number 10/727,195 is a Non-Final Office Action mailed September 29, 2008.

**Supplemental IDS**

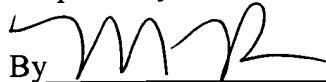
Applicants provide herewith a Supplemental Information Disclosure Statement.

**CONCLUSIONS**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for the same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945 under order number CIBT-P01-104.

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Respectfully submitted,

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